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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER

HM12/0306

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G.E. EHRLICH (1995) LTD. C/O ANTHONY CAS
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ART UNIT

PAPER NUMBER

1638

DATE MAILED:

03/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/411,863

Applicant(s)

IZHAR, SHAMAY

Examiner

Anne Kubelik

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 January 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-55 is/are pending in the application.
- 4a) Of the above claim(s) 1-9, 11-46 and 48 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 10, 47 and 49-55 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 04 October 1999 is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 18) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: _____

DETAILED ACTION

1. Applicant's election of Group IV (claims 10, 47 and 49-55) in Paper No. 5 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
2. The following claim errors are noted:

In claim 53, an article should be inserted between "generates" and "male."

In claim 54, "offsprings" should be "offspring;" both the singular and plural forms of the word are the same. Also in that claim, the first "by" should be deleted.
3. Examiner wishes to remind Applicant that "it's" is a shortened form of "it is" and that the correct word for the possessive is "its."
4. On page 29, line 5 of the specification is the word "orgcharacterized." Clarification or correction is required.

Drawings

5. The drawings are objected to for the reasons indicated in form PTO 948. Correction is required.

Claim Objections

6. Claims 10, 47 and 49-51 are objected to because they are dependent on nonelected claims. Appropriate correction is required.
7. Applicant is advised that should claim 10 be found allowable, claim 52 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing,

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despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 47 and 49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to methods of generating exogenic allelism in a plant via introduction of a recombinase protein into one or two plants that are homozygous for a particular expression cassette, then crossing the resulting progeny. The instant specification, however, fails to provide guidance for application of a recombinase protein into an organism to result in a DNA segment being excised and for avoiding problems caused by recombination between homologous chromosomes in plants homozygous for the recombination sequence-containing cassettes.

The instant specification fails to provide guidance for application of a recombinase protein to an organism, getting the applied protein, and for having it reliably result in specific recombination.

When the recombinase is introduced into an organism via transformation of the gene that encodes it or via crossing with another individual that has the gene that encodes it, unexpected results can be seen when the organism is homozygous for the recombination sequence (*i.e.*, has

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the sequence on both chromosomes of a pair). Qin et al (1994, Proc. Natl. Acad. Sci. USA 91:1706-1710) teach that the *cre* recombinase can produce translocations when *lox* sites are located on different chromosomes (pg pg 1709, right column, paragraph 1). Golic (1991, Science 252:958-961) teaches that the FLP recombinase will induce recombination between homologous chromosomes, generating mosaics (abstract). In the instant application, this would be a problem, and the specification lacks guidance for its avoidance.

Additionally, the FLP/FRT recombination system does not work reliably in all plants. Lloyd et al (1994, Mol. Gen. Genet. 242:653-657) teach that FLP/FRT recombination did not work in *Arabidopsis* (pg 657, left column, paragraph 2). Luo et al (2000, Plant J. 23:423-430) teach that in order to get the FLP/FRT recombination system to work in *Arabidopsis*, use of a FLP gene sequence with a variation in the sequence just upstream of the ATG initiation codon was required (paragraph spanning pg 427-428). The instant specification lacks guidance for overcoming this problem.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate methods for generating exogenic allelism in a plant, via non-transformation-mediated or transformation-mediated introduction of a recombinase protein into one or two plants that are homozygous for a particular expression cassette, then crossing the resulting progeny.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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11. Claim 52 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 52 is indefinite in the recitation of the word "including." It is unclear if this word is intended to be open or closed. If open language is intended, the word should be replaced with --comprising--.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 10, 52 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Vergunst et al (1998, Nuc. Acids Res. 26:2729-2734).

Vergunst et al teach plants that have different exogenes in an allelic relationship on two chromosomes of a pair (pg 2732, paragraph spanning the columns, and pg 2733, right column, paragraph 1). These genes would inherently segregate to different gametes.

14. Claims 10 and 52-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Fabijanski et al (1995, US Patent 5,426,041).

Fabijanski et al teach plants that have two different exogenes in an allelic relationship, are male-sterile, and when crossed to a male-fertile plant would produce male-fertile offspring (column 15, line 48, to column 16, line 63, and Claims 9-10).

15. Claim 50 is rejected under 35 U.S.C. 102(b) as being anticipated by Lloyd et al (1994, Mol. Gen. Genet. 242:653-657).

Lloyd et al teach plants that are homozygous for a construct that has, in the following order, a 35S promoter, an FRT recombination sequence, a second promoter operably linked to an ampicillin resistance gene, another FRT recombination sequence, and an Hyg gene (Figs 1 and 2, table 1, and pg 654, right column).

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

17. Claims 10 and 52-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vergunst et al (*supra*) in view of each of Fabijanski et al (*supra*) and Mariani et al (1990 Nature 347:737-741).

The claims are drawn to plants that have different exogenes in an allelic relationship on two chromosomes of a pair, where the exogenes are selected so that plants are male sterile.

Vergunst et al disclose teach plants that have different exogenes in an allelic relationship on two chromosomes of a pair (pg 2732, paragraph spanning the columns, and pg 2733, right

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column, paragraph 1). These genes would inherently segregate to different gametes, as discussed above. Vergunst et al do not disclose selection of the exogenes such that the plants are male sterile.

Fabijanski et al teach plants that have exogenes that result in male-sterile plants that can be restored to fertility by crossing (column 15, line 48, to column 16, line 63).

Mariani et al teach the male sterility system TA29-barnase and its use to make male-sterile plants (pg 738-740).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to produce plants that have different exogenes in an allelic relationship on two chromosomes of a pair as taught by Vergunst et al and to modify that to use a male sterility system as described in each of Fabijanski et al and Mariani et al. One of ordinary skill in the art would have been motivated to do so because of the benefit of male sterility systems in production of hybrid plants (Mariani et al, pg 737, left column, paragraph 2) and the desirability of gene targeting to eliminate variation in gene expression (Vergunst et al, pg 2729, right column, paragraph 1).

18. Claims 47 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hodges et al (US Patent 5,929,307, 102(e) date December, 1996) in view of Medberry et al (1995, Nuc. Acids Res. 23:485-490).

The claims are drawn to method of generating exogenic allelism via use of a recombination system, and a plant used in the method.

Hodges et al disclose a method of using a recombination system in plants that utilizes plants homozygous for a particular construct that are crossed to recombinase-gene containing

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plant (column 20, lines 1-35). Some of the resulting progeny would have the original construct on one chromosome and the excised construct on the other chromosome. Hodges also teach a male sterility system (column 4, line 35, to column 6, line 55). Hodges et al do not the use of constructs with two promoters.

Medberry et al teach a construct that has the following in the following order: a promoter, a recombination sequence, a second promoter, a gene, another recombination sequence, another gene (Fig. 1).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to use the method of generating plants with exogenic allelism as taught by Hodges et al and to modify that to use plants transformed with the constructs described in Medberry et al. One of ordinary skill in the art would have been motivated to do so as part of the fine-tuning required in operation of the system.

19. Claims 49 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vergunst et al in view of each of Fabijanski et al and Mariani et al as applied to claims 10 and 52-55 above, and further in view of Snaith et al (1995, Gene 166: 173-174) and Lloyd et al (1994, Mol. Gen. Genet. 242:653-657).

The claims are drawn to a method of generating exogenic allelism via use of two different recombination systems, and a plant used in the method.

Vergunst et al in view of each of Fabijanski et al and Mariani et al disclose plants with exogenes that result in male sterility and that are in an allelic relationship on two chromosomes of a pair. Vergunst et al in view of each of Fabijanski et al and Mariani et al do not disclose the use of two different recombination systems in the production of those plants.

Snaith et al teach plasmids with multiple FRT and *loxP* sites, suggest their use in combined manipulation strategies, and discuss their importance as tools in *in vivo* manipulation of DNA (Fig 1 and pg 173, right column, and abstract).

Lloyd et al suggest expressing two different site-specific recombination systems in the same plant (pg 653, right column, 1st full paragraph).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to produce plants with exogenes that result in male sterility and that are in an allelic relationship on two chromosomes of a pair as taught by Vergunst et al in view of each of Fabijanski et al and Mariani et al, and to modify that to use plasmids with both FRT and *loxP* sites as described in Snaith et al. One of ordinary skill in the art would have been motivated to do so because of the suggestion of Lloyd et al to use more than one site-specific recombination system in the same plant (pg 653, right column, 1st full paragraph).

20. Claims 49 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hodges et al (*supra*) in view of Snaith et al (1995, Gene 166: 173-174), and further in view of Lloyd et al (1994, Mol. Gen. Genet. 242:653-657).

The claims are drawn to a method of generating exogenic allelism via use of two different recombination systems, and a plant used in the method.

Hodges et al disclose a method of using a recombination system in plants that utilizes plants homozygous for a particular construct that are crossed to recombinase-gene containing plant (column 20, lines 1-35). Some of the resulting progeny would have the original construct on one chromosome and the excised construct on the other chromosome. Hodges et al do not teach the use of two different recombination systems in that method.

Snaith et al teach plasmids with multiple FRT and *loxP* sites, suggest their use in combined manipulation strategies, and discuss their importance as tools in *in vivo* manipulation of DNA (Fig 1 and pg 173, right column, and abstract).

Lloyd et al suggest expressing two different site-specific recombination systems in the same plant (pg 653, right column, 1st full paragraph).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to method of generating exogenic allelism via use of a single recombination system as taught by Hodges et al and to modify that to use two recombination systems as described in Snaith et al. One of ordinary skill in the art would have been motivated to do so because of the suggestion of Lloyd et al to use more than one site-specific recombination system in the same plant (pg 653, right column, 1st full paragraph).

Conclusion

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached on Monday through Friday, 8:15 am - 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Anne R. Kubelik, Ph.D.
March 2, 2001

DAVID T. FOX
PRIMARY EXAMINER
GROUP 180-1638

